EDITORIAL (SEE SOSENKO ET AL., P. 528)

Should We Screen for Risk of Type 1 Diabetes?

Thus far, the consensus within the diabetes community has been that we should screen for risk of type 1 diabetes only in the context of research studies. This view follows the World Health Organization recommendation on screening of clinical conditions, which states that you should screen only for diseases for which there is effective prevention or treatment (1). Data from the DAISY study suggest that the identification of subjects at increased risk for type 1 diabetes and prospective monitoring of risk individuals results in early diagnosis of clinical disease and the avoidance of severe metabolic decompensation at diagnosis among those who progress to overt diabetes (2). The Finnish DIPP Study has generated similar experiences by reducing the frequency of diabetic ketoacidosis at diagnosis from 20 to <2% (K. Näntö-Salonen, H. Hyöty, J. Ilonen, R. Veijola, T. Simell, M. Knip, and O. Simell, unpublished data). Given that diabetic ketoacidosis is a potentially life-threatening condition and that severe metabolic decompensation at diagnosis is associated with a reduced residual β-cell function and impaired metabolic control subsequently (3,4), one may ask whether it would be meaningful to screen for high-risk individuals and monitor them sequentially for progression to type 1 diabetes.

In this issue, Sosenko et al. (5) introduce a risk score for type 1 diabetes derived from the Diabetes Prevention Trial–Type 1 (DPT-1) (5). The authors divided the DPT-1 cohort into development and validation samples. From the former, a risk score was established based on a model including the logarithm of BMI, age, the logarithm of fasting C-peptide, and total glucose and C-peptide sums from a 2-h oral glucose tolerance test (OGTT). This risk score strongly predicted type 1 diabetes in the validation sample. The predictive value of the risk score did not increase by including a reduced first-phase insulin response (FPIR) from an intravenous glucose tolerance test (IVGTT) as a predictor. A final risk score was derived from all participants based on the variables listed above. The change in risk score from baseline up to 1 year was also highly predictive of type 1 diabetes. The authors conclude that a risk score based on age, BMI, and OGTT indexes appears to accurately predict type 1 diabetes in islet cell autoantibody (ICA)-positive relatives of affected patients.

The authors admit that their risk score has its limitations. First of all, it is based an a group of relatives whose selection was contingent on ICA positivity, and, accordingly, the extent to which the risk score is applicable to relatives identified through autoantibodies other than ICA or to ICA-negative relatives remains a question. Second, the application of the risk score requires that the glucose and C-peptide assays are identical with those used in the DPT-1 study. The DPT-1 cohort comprised both first- and second-degree relatives, and as a consequence it is quite heterogenous, although the authors assure that the risk score was highly predictive in both groups of relatives. BMI remained a significant predictor in the stepwise proportional hazards regression, which implies that increasing insulin resistance would be associated with an enhanced risk of type 1 diabetes. Such an observation indirectly supports the accelerator hypothesis (6) claiming that weight gain partly explains the increasing incidence of type 1 diabetes among children under the age of 15 years seen in most developed countries after World War II. Sosenko et al. (5) also performed the homeostasis model assessment of insulin resistance and observed that this variable did not predict type 1 diabetes, although relative insulin resistance (homeostasis model assessment of insulin resistance/FPIR) was associated with progression to type 1 diabetes in the initial univariate analysis. Two previous studies have reported that relative insulin resistance does confer increased risk for development of type 1 diabetes in autoantibody-positive first-degree relatives (7,8). The reason for the seemingly contrasting results may be that BMI turned out to be a significant predictor in the risk score presented by Sosenko et al., thereby excluding relative insulin resistance, since there is a relatively strong correlation between BMI and insulin resistance.

A previous report based on the Childhood Diabetes in Finland study has generated a prognostic risk index in siblings of affected children (8). In that cohort (including all siblings irrespective of autoantibody status), young age, an increasing number of autoantibodies and of affected family members at initial screening, and HLA-conferred disease susceptibility were associated with an increased risk of type 1 diabetes. In a subgroup of autoantibody-positive siblings, young age, HLA-defined diabetes predisposition, an increasing number of autoantibodies, a reduced FPIR, and decreased insulin sensitivity in relation to FPIR predicted progression to clinical diabetes.

What is common and what divergent between the risk score by Sosenko et al. (58)? Young age is a common feature, with both sets of authors emphasizing that initiation of the disease process early in life results in rapid progression to overt disease. A reduced FPIR was a significant predictor of type 1 diabetes in both studies, although the FPIR was not included in the final risk score by Sosenko et al., who also concluded that IVGTTs may not contribute much predictive information beyond that obtained from OGTTs. That statement may be correct, but one might ask whether the individual at risk prefers a 10-min IVGTT or a 120-min OGTT.

What, then, are the differences between the risk score and risk index? Other autoantibodies were not included in the risk score, whereas the number of detectable autoantibodies contributed to the risk index. This divergence may be related to the initial inclusion criterion: ICA positivity in the American study (5) and any autoantibody positivity in the Finnish subcohort (8). The DPT-1 observation would indicate that other autoantibodies do not substantially add to the predictive value of ICA, whereas the Finnish study suggests that the number of autoantibodies is the autoantibody marker with the strongest predictive value. HLA-conferred disease susceptibility was not considered as a potential predictor in the DPT-1–based study, whereas it turned

out to be a significant predictor in the Finnish series.

Is there a rationale beyond research studies for screening siblings of affected subjects who have a relative risk of type 1 diabetes at least 10 times higher than that in the general population (with the absolute risk in the range of 6 to 10% [9])? What would be the optimal screening strategy? The analysis of autoantibodies to biochemically characterized autoantigens, i.e., insulin, GAD, and islet antigen 2, provides the most sensitive and specific tool for prediction of type 1 diabetes among siblings. Positivity for two autantibodies is associated with a cumulative disease risk of >80% over the next 15 years (10) and positivity for three autoantibodies with an even higher progression rate (11). The arguments in favor of screening siblings have been listed above. What, then, are the potential drawbacks of such an approach? One consideration is that all autoantibody-positive siblings do not progress to clinical diabetes over a reasonable time of follow-up, and the knowledge of autoantibody positivity likely has a psychological impact on both the individual and the family (12) and may result in behavioral changes in an effort to prevent or delay progression to clinical disease (13). This is, however, an area of research that needs to be scientifically assessed in a more rigorous manner. Another issue is the costs associated with screening and subsequent monitoring of siblings identified to be at high risk of type 1 diabetes. There is a definite need for a cost-benefit analysis of any screening program before its clinical implementation.

What about screening the general population for type 1 diabetes in high-incidence countries? Again, the strategy for such a screening program can already be designed based on present knowledge. With HLA genotyping, it is possible to identify a group of individuals at similar risk for type 1 diabetes as siblings of affected children (14). Children with HLA-conferred disease susceptibility might subsequently be monitored for the appearance of disease-associated autoantibodies and progression to clinical diabetes. As already shown, this would result in a dramatic decrease in the frequency of diabetic ketoacidosis at diagnosis and thus, most likely, to shorter initial hospitalization and better preservation of endogenous insulin secretion among those who present with clinical diabetes. Since severe diabetic ketoacidosis is a life-threatening condition, some deaths could also be prevented by such a screening program.

HLA genotyping should be performed very early in life, preferably at birth, since the first autoantibodies may appear during the first year (15). If the screening program is initiated, for example, at a mean age of 10 years, at least 60% of children diagnosed before the age of 15 years would have already presented with overt type 1 diabetes. Given the considerable costs associated with a screening and monitoring program in the general population, we probably have to wait for the establishment of effective prevention strategies before any such program will be implemented even in high-incidence countries.

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Abbreviations: DPT-1, Diabetes Prevention Trial–Type 1; FPIR, first-phase insulin response; islet cell autoantibody; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

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